PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 3839PTWO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/051230	International filing date *(day/month/year)* 24.06.2004	Priority date *(day/month/year)* 26.06.2003
International Patent Classification (IPC) or national classification and IPC A61K9/22		
Applicant MEDIOLANUM PHARMACEUTICALS LTD. et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 6 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 3 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.04.2005	24.01.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Muller, S Telephone No. +31 70 340-2080

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/051230

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-26	as originally filed
Claims, Numbers	
1-21	received on 25.04.2005 with letter of 20.04.2005
Drawings, Sheets	
1/17-17/17	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-21
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-21
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. Cited Documents

The following documents are referred to in this communication:

D1: PHARMACEUTICAL RESEARCH, vol. 13, no. 7, 1996, pages 1059-1064, XP008036235

D2: WO 03/094888 A (ASHTON PAUL ;CHOU KANG-JYE (US); GUO HONG (US); CONTROL DELIVERY S) 20 November 2003 (2003-11-20)

D3: WO 00/33809 A (MARION PIERRE ;MAQUIN ALAIN (FR); MAURIAC PATRICE (FR); MEDIOLANUM) 15 June 2000 (2000-06-15) (cited by the Applicant)

2. Novelty

D1 discloses (see page 1059, column 2, line 38 - page 1069, column 1, line 31) implants which are made by compression of granules of 5-Fluorouracil dispersed in PLGA polymers. The matrix implants are dip-coated with the same polymer as used in the manufacture of the matrix implant.
The core disclosed in claim 1 differs from that of D1 in that it is obtained by extrusion instead of compression of granules. The structure of the core claimed in the present application has therefore a continuous and homogenous structure, whereas the core disclosed in D1 is formed by discrete granules mechanically aggregated through compression means.
The subject-matter of independent claims 1,13 and 21 is therefore not new in view of D1 (Article 33 (2) PCT).

No document of the prior art discloses an implant comprising a) a core comprising a drug in a PLGA matrix obtained by extrusion and b) a coating comprising as the main component PLGA.
The subject-matter of the present application therefore appears to be new over the prior

art (Article 33(2) PCT).

3. Inventive Step

D3 is considered as being the closest prior art.
It discloses (see page 3, line 32 - page 7, line 2) subcutaneous implants prepared by extrusion containing a peptide dispersed in a matrix of polylactic-glycolic acid.
The subcutaneous implant disclosed in the current application differs from that of D3 in that the implant further comprises a coating in film form comprising PLGA as main component.
The effect of this difference is that the first burst which occurs in the first days after insertion of the implant as well as the second burst caused by the disintegration of the core are reduced.
The objective problem of the application may therefore be regarded as the provision of an improved subcutaneous implant prepared by extrusion comprising an active ingredient in a PLGA matrix and having reduced first and second burst effects.
No document of the prior art suggests the addition of a coating comprising PLGA as main component around a core comprising a drug in a PLGA matrix in order to have reduced first and second burst effects.
The present application therefore appears to be inventive over the prior art (Article 33(3) PCT).

4. Industrial applicability

Claims 1-21 satisfy the criterion of industrial applicability set forth in Article 33(4) PCT.

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.
PCT/EP2004/051230

W0-03094888	20 November 2003	1 May 2003	7 May 2002 31 December 2002 6 March 2003

(71)

NEW SET OF CLAIMS

1. Subcutaneous implants comprising:

- a core (i) comprising at least one active principle dispersed in a polymeric matrix essentially consisting of PLGA obtained by extrusion,
- a coating (ii) in film form comprising as the main component PLGA,

2. Subcutaneous implant as claimed in claim 1, wherein the active principle contained in the core (i) is chosen from the class consisting of: a peptide, an active principle able to increase bone density, an analgesic-narcotic, a steroid hormone for hormonal treatments during menopause or for contraception.

3. Subcutaneous implant as claimed in claim 2, characterised in that when the core (i) contains a peptide the particles of said active principle present extremely heterogeneous dimensions which vary from 1 micron to 63 microns.

4. Subcutaneous implants as claimed in any one of claims 1-3, characterised in that the PLGA used in the core (i) preferably presents a molecular weight between 50,000 and 150,000 and a molar ratio of lactic acid to glycolic acid monomers between 50:50 and 95:5.

5. Subcutaneous implants as claimed in anyone of claims 1-4, wherein the coating (ii) contains PLGA in amounts ranging from 75 to 99,999% and the remaining to 100 essentially consisting of excipients and/or of the same active ingredient used in the core (i).

6. The subcutaneous implants according to claim 5, wherein the coating (ii) essentially consists of PLGA.

7. The subcutaneous implants according to claim 5, wherein the coating (ii) consists of a mixture of 80%PLGA and the remaining to 100% of at least one hydrophilic excipient .

8. The subcutaneous implants according to claim 7, wherein said hydrophilic excipient is selected from the group consisting of polyvinyl pyrrolidone, D-mannitol and mixtures thereof.

9. The subcutaneous implants according to claim 5, wherein the coating (ii) consists of a mixture of 75% PLGA and the remaining to 100% of the same active ingredient contained in the core (i).

10. Subcutaneous implant as claimed in any one of claims 1-9, characterised in

that said coating in film form (ii) consists of PLGA with a molecular weight between 50,000 and 150,000 and a molar ratio of lactic acid to glycolic acid monomers between 50:50 and 95:5.

11. Subcutaneous implant as claimed in claim 10, wherein said PLGA presents an average molecular weight between 100,000 and 150,000 and said molar ratio is comprised between 50/50 and 75/25.

12. Subcutaneous implant as claimed in any one of claims 1-11, characterised in that the coating (ii) presents a thickness between 5 and 250 µm.

13. Subcutaneous implant as claimed in claim 12, wherein said thickness is comprised between 10 and 100 µm.

14. Process for preparing the subcutaneous implants as claimed in anyone of claims 1-13, comprising the following stages:

a) preparing the core (i) containing the active principle by extrusion,

b) passing the core (i) into a solution of PLGA in a suitable solvent chosen from apolar and aprotic polar solvent such that said cores remain in contact with said solution for a period between 1 and 5 seconds,

c) drying said cores originating from stage (b).

15. Process as claimed in claim 14, wherein the apolar solvent is a chlorinated solvent.

16. Process as claimed in claim 15, characterised in that said solvent is methylene chloride.

17. Process as claimed in claim 14, wherein said aprotic polar solvent is chosen from acetonitrile, ethyl acetate, tetrahydrofuran.

18. Process as claimed in any one of claims 14-17, wherein the PLGA concentration in the solution used in stage (a) is comprised between 70 and 300 g/l.

19. Process as claimed in claim 18, wherein said concentration is comprised between 100 and 200 g/l.

20 . Process as claimed in any one of claims 14-19, characterised in that said contact time is 1 second.

21. Process for preparing the subcutaneous implant in according to any one of claims 1-13 comprising the following stages:

a') mixing the active principle with PLGA,

b') possibly granulating the mixture originating from (a') in the minimum solvent quantity, and drying the granules obtained,

c') co-extruding the mixture originating from (a') or from (b') together with the PLGA used for preparing the coating in film form (ii).